ISSN 1070-3632, Russian Journal of General Chemistry, 2017, Vol. 87, No. 1, pp. 154–155. © Pleiades Publishing, Ltd., 2017.
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LETTERS TO THE EDITOR

Synthesis of 9-Aryl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-diones

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Received August 25, 2016

Abstract—The reaction in a mixture of 1,3-cyclohexanedione (dimedone), arylaldehyde, and ammonium acetate at 160°C during 10–15 min in the absence of solvent leads to the formation of 9-aryl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-diones. The structure of the products has been confirmed by IR and ^{1}H NMR spectroscopy data. Antimicrobial activity of the obtained compounds has been studied.

Keywords: 9-aryl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione, Hantzsch synthesis, antimicrobial activity
DOI: 10.1134/S107036321701025X

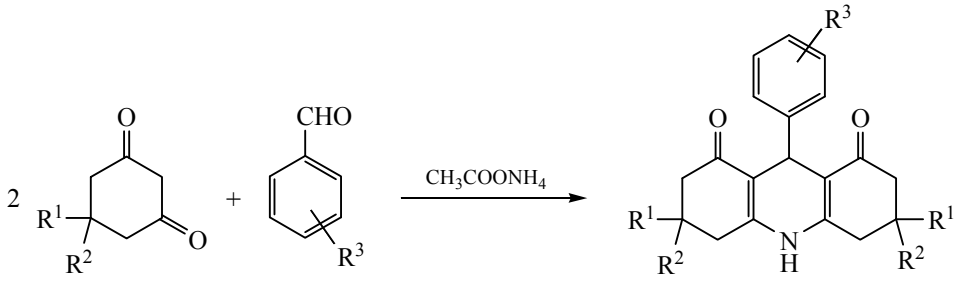
Acridine and its analogs have been recognized for antimicrobial activity [1]. Hantzsch reaction is used for the preparation of 9,10-disubstituted decahydroacridine-1,8-diones [2]. This synthesis includes two stages: the interaction of a cyclic 1,3-diketone with an aldehyde affording Michael adduct and its heterocyclization with a primary amine. A single-stage preparation of such compounds via refluxing a mixture of dimedone, an aldehyde, and a primary amine in DMF medium in the presence of hydrochloric acid has been suggested in [3]. This method of hexahydroacridine-1,8(2*H*,5*H*)-diones synthesis is simple, fast, and gives the target product in a good yield.

We found that keeping a mixture of 1,3-cyclohexanedione, arylaldehyde, and ammonium acetate at 160°C during 10–15 min in the absence of solvent afforded 9-aryl-3,4,6,7, 9,10-hexahydroacridine-1,8(2*H*,5*H*)-diones **1a–1e** (Scheme 1).

Compounds **1a–1e** were pale yellow crystalline substances, soluble in DMF, DMSO, and ethanol (at heating) and insoluble in water.

IR spectra of the prepared compounds contained the bands of carbonyl group stretching vibrations (1640–1648 cm^{-1}), C=C bonds stretching vibrations (1596–1612 cm^{-1}), and heterocyclic N–H stretching vibrations (3176–3192 cm^{-1}). Besides the signals of aromatic protons, a singlet of the H^9 proton (4.65–4.90 ppm), and the NH proton signal (8.36–9.56 ppm), ^{1}H NMR spectra of compounds **1d** and **1e** contained singlet signals of protons of four methyl groups in positions 3

Scheme 1.



1a–**1e** (78–81%)

$R^1 = R^2 = H$, $R^3 = Cl$ (**a**); $R^1 = R^2 = H$, $R^3 = MeO$ (**b**); $R^1 = R^2 = H$, $R^3 = 3\text{-}NO_2$ (**c**); $R^1 = R^2 = CH_3$, $R^3 = MeO$ (**d**); $R^1 = R^2 = CH_3$, $R^3 = Cl$ (**e**).

and 6 of the heterocycle (0.84–0.86, 1.03–1.05 ppm), four doublets of protons at the C^2, C^7 and C^4, C^5 atoms (1.96–2.40 ppm) with spin-spin coupling constant 16.5 Hz, and the spectra of compounds **1a–1c** contained multiplets of four protons at the C^2 and C^7 atoms (2.05–2.48 ppm), the C^4 and C^5 atoms (1.81–2.25 ppm), C^3 and C^6 atoms (1.69–1.92 ppm). The signals multiplicity was determined by the presence of a chiral center in the position 9 of the molecules, making the protons in positions 2, 4, 5, and 7 enantiotropic.

The spectral data showed that compounds **1a–1e** existed in the keto form with the proton localized at the nitrogen atom.

Antimicrobial activity of compounds **1a–1e** was determined using a method of twofold serial dilution in a liquid medium. Minimal suppressing concentrations MSC (μg/mL) against the *S. aureus* ATCC 6538 and *E. coli* ATCC 25922 strains [4] were determined. MSC of the studied compounds was 1000 μg/mL, whereas the MSC of a reference drug Dioxidine was 62.5–1000 μg/mL against *S. aureus* ATCC 6538 and 3.9–6.2 μg/mL against *E. coli* ATCC 25922. Hence, compounds **1a–1e** exhibited low antimicrobial activity.

9-(4-Chlorophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (1a). A mixture of 0.02 mol of 1,3-cyclohexanedione, 0.01 mol of aromatic aldehyde, and 0.01 mol of ammonium acetate was kept during 10–15 min at 150–160°C until gas evolution had ceased and the reaction mixture became solid. After cooling, the solid residue was treated with ethanol, filtered, and recrystallized from ethanol. Yield 2.73 g (76%), mp >300°C. IR spectrum, ν, cm^{-1}: 1604 (C=C), 1644 (C=O), 3176 (NH). ^{1}H NMR spectrum, δ, ppm: 2.15–2.26 m (4H, C^2H_2, C^7H_2), 1.87–1.95 m (4H, C^4H_2, C^5H_2), 1.75–1.83 m (4H, C^3H_2, C^6H_2), 4.82 s (1H, C^9H), 6.92–7.36 m (4H, Ar), 9.36 s (1H, NH). Found, %: C 69.62; H 5.53; N 4.27. $C_{22}H_{14}NO_2Cl$. Calculated, %: C 69.52; H 5.43; N 4.37.

9-(4-Methoxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (1b). Yield 2.77 g (78%), mp 273–275°C. IR spectrum, ν, cm^{-1}: 1612 (C=C), 1648 (C=O), 3176 (NH). ^{1}H NMR spectrum, δ, ppm: 2.15–2.26 m (4H, C^2H_2, C^7H_2), 1.83–1.91 m (4H, C^4H_2, C^5H_2), 1.69–1.78 m (4H, C^3H_2, C^6H_2), 3.70 s (3H, OCH_3), 4.87 s (1H, C^9H), 7.12–7.92 m (4H, Ar), 9.56 s (1H, NH). Found, %: C 74.28; H 6.55; N 4.33. $C_{23}H_{17}NO_3$. Calculated, %: C 74.58; H 6.85; N 4.13.

9-(3-Nitrophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (1c). Yield 2.97 g (80%), mp. >300°C. IR spectrum, ν, cm^{-1}: 1608 (C=C), 1640 (C=O), 3184 (NH). ^{1}H NMR spectrum, δ, ppm: 2.10–2.23 m (4H, C^2H_2, C^7H_2), 1.87–1.96 m (4H, C^4H_2, C^5H_2), 1.71–1.83 m (4H, C^3H_2, C^6H_2), 4.90 s (1H, C^9H), 7.20–7.92 m (4H, Ar), 9.54 s (1H, NH). Found, %: C 67.45; H 5.36; N 8.18. $C_{22}H_{14}N_2O_4$. Calculated, %: C 67.15; H 5.53; N 7.98.

3,3,6,6-Tetramethyl-9-(4-methoxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (1d). Yield 2.95 g (78%), mp 273–275°C. IR spectrum, ν, cm^{-1}: 1596 (C=C), 1644 (C=O), 3192 (NH). ^{1}H NMR spectrum, δ, ppm: 0.84 s and 1.052 s (12H, CH_3), 1.96 d (2H, C^4H_2, J = 16.5 Hz), 2.11 d (2H, C^5H_2, J = 16.5 Hz), 2.32 d (2H, C^2H_2, J = 16.5 Hz), 2.38 d (2H, C^7H_2, J = 16.5 Hz), 3.65 s (3H, OCH_3), 6.52–7.06 m (4H, Ar), 8.36 s (1H, NH). Found, %: C 75.96; H 7.70; N 3.69. $C_{24}H_{29}NO_3$. Calculated, %: C 75.81; H 7.89; N 3.85.

3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (1e). Yield 3.10 g (81%), mp >300°C. IR spectrum, ν, cm^{-1}: 1596 (C=C), 1644 (C=O), 3192 (NH). ^{1}H NMR spectrum, δ, ppm: 0.86 s and 1.042 s (12H, CH_3), 1.98 d (2H, C^4H_2, J = 16.5 Hz), 2.08 d (2H, C^5H_2, J = 16.5 Hz), 2.29 d (2H, C^2H_2, J = 16.5 Hz), 2.41 d (2H, C^7H_2, J = 16.5 Hz), 4.67 s (1H, C^9H), 6.50–7.10 m (4H, Ar), 8.41 s (1H, NH). Found, %: C 71.96; H 6.83; N 3.65. $C_{23}H_{26}NO_2Cl$. Calculated, %: C 71.72; H 6.53; N 3.35.

^{1}H NMR spectra were recorded using a Bruker DRX-500 instrument (500.13 MHz) in DMSO-d_6 with TMS as internal reference. IR spectra (KBr pellets) were recorded using a Specord M-80 spectrophotometer. Elemental analysis was performed using a Perkin Elmer 2400 instrument. Melting points were determined using a Melting Point M-565 instrument. The reaction progress and the products purity were monitored by means of TLC on Silufol UV-254 plates in a $CHCl_3$–AcOH (9 : 1) system developing with UV irradiation.

ACKNOWLEDGMENTS

This work was financially supported by the Russian Science Foundation (project no. 15-13-10029).

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